Effect of Potassium Chloride on the Blood Pressure in Two-Kidney, One Clip Goldblatt Hypertensive Rats

HIROMICHI SUZUKI, M.D., KAZUOKI KONDO, M.D., AND TAKAO SARUTA, M.D.

SUMMARY The effects of potassium loading on blood pressure (BP) and the renin-angiotensin-aldosterone system were investigated in two-kidney, one clip Goldblatt hypertensive rats. Two series of experiments were performed: one was begun just after renal artery constriction, and the other, after hypertension had developed. Potassium loading significantly attenuated the development of hypertension, and was also able to abate existing renovascular hypertension. In both studies, potassium loading increased fluid intake and urine volume, which were accompanied by increased excretion of sodium and potassium. In spite of the massive diuretic effect, potassium loading significantly attenuated the increased plasma renin activity (PRA) induced by renal artery constriction, while it further enhanced the increased plasma aldosterone concentration (PAC) in two-kidney, one clip Goldblatt hypertensive rats. There was no significant difference in the values of serum sodium and potassium between the two groups with or without potassium loading. These results suggest that potassium may attenuate the development of hypertension and reduce the elevated BP by diuresis and natriuresis and by suppression of the PRA in two-kidney, one clip Goldblatt hypertensive rats.

(Hypertension 3: 566-573, 1981)

KEY WORDS • potassium loading • blood pressure • renin-angiotensin-aldosterone system • two-kidney, one clip Goldblatt hypertension

M ANY previous reports stated that potassium has antihypertensive properties. The diuretic action of potassium had already been described in 1679, and, indeed, the usefulness of Kempner's rice fruit diet for the therapy of hypertension was demonstrated. In addition to its well-established diuretic effect, this substance has been reported to exert direct vasodilator effects and to attenuate vascular contractions induced by vasoactive substances. Furthermore, Douglas et al. reported that potassium is able to suppress plasma renin activity (PRA) directly.

Although potassium has been accredited with these various antihypertensive effects, its precise antihypertensive mechanism still remains uncertain. In the present experiments in rats, we studied the depressor effect of potassium in established two-kidney, one clip Goldblatt hypertension and its preventive effect in the development of this type of hypertension.

Materials and Methods

Male Wistar rats, weighing 190 to 210 g, were anesthetized with ether, and the left kidney was exposed through a mid-line incision in the skin of the back; a silver clip, 0.2 mm in width, was placed on the left renal artery. All rats were maintained in humidity- and temperature-controlled quarters, each rat being housed in a metabolic cage.

Systolic blood pressure (BP) was measured by a tail plethysmographic method twice a week. The daily fluid intake and urine volume were measured, and the urinary excretions of sodium and potassium were determined every other day during the study. The PRA was determined by the method of Skinner, and plasma aldosterone concentration (PAC) by radioimmunoassay. Serum and urinary electrolytes were measured with a flame photometer.

Fifteen rats were killed by decapitation to obtain control values for PRA, PAC, and serum sodium and potassium before the beginning of the study.

Experiment 1

Rats with a clip placed on the left renal artery and an untouched contralateral kidney were divided into two groups of 45 animals each. An additional group of
45 rats was subjected to sham-clipping: the left renal artery was exposed, and a silver clip was placed in the perinephric fat. The rats in Group 1 and in the sham-operated group received tap water to drink, and the rats in Group 2 received a 0.5% KCl (0.06 mole/liter) solution to drink. All animals were fed a normal diet containing 0.28 g% Na and 0.77 g% K. On Days 7, 14, and 28 of the experiment, 15 rats of each group were killed by decapitation, blood was collected into test tubes, and determinations of PRA, PAC, and serum sodium and potassium were made.

Experiment 2

Two groups of 30 rats each (Groups 3 and 4) were operated on as in Experiment 1. After the operation, both groups received tap water to drink for the first 2 weeks. Then 15 rats of each group were sacrificed by decapitation, blood was collected into chilled tubes, and the PRA, PAC, and serum sodium and potassium were measured. The remaining rats of Group 3 received tap water to drink, but those of Group 4 were switched to 0.5% KCl (0.06 mole/liter) solution to drink. Two weeks later (4 weeks after the operation), all the rats were killed, blood was collected into chilled tubes, and the PRA, PAC, and serum sodium and potassium were measured.

The results were expressed as means ± standard deviation. Statistical analysis of the data was performed using Student's t test.

Results

Experiment 1

Systolic Blood Pressure

The systolic BP of two-kidney, one clip Goldblatt hypertensive rats in Group 1 (without potassium loading) increased and attained levels of 180 to 200 mm Hg by the end of the experiment (4 weeks after the operation). As shown in figure 1, potassium loading significantly attenuated the elevation of BP induced by renal artery constriction (p < 0.05). There was no elevation of the systolic BP in sham-operated rats.

Body Weight

There was no difference in growth among the three groups during the study [untreated = 200 ± 8 g (before) to 282 ± 6 g (28th day); treated with 0.5% KCl = 200 ± 6 g (before) to 276 ± 4 g (28th day); sham-operated = 202 ± 6 g (before) to 280 ± 2 g (28th day)].

Fluid Intake, Urine Volume, Urinary Excretion of Sodium and Potassium, and Serum Sodium and Potassium

In two-kidney, one clip Goldblatt hypertensive rats, fluid intake and urine volume gradually increased during the first week and reached a plateau in the second week. There was no significant difference in fluid intake and urine volume between two-kidney, one clip Goldblatt hypertensive rats and sham-operated rats. As shown in figure 2, both fluid intake and urine volume were further increased by potassium loading. In addition, potassium loading resulted in increased urinary excretion of sodium and potassium (fig. 3). There was no significant difference in urinary excretion of sodium and potassium between two-kidney, one clip Goldblatt hypertensive rats and sham-operated rats. As shown in figure 2, both fluid intake and urine volume were further increased by potassium loading. In addition, potassium loading resulted in increased urinary excretion of sodium and potassium (fig. 3). There was no significant difference in urinary excretion of sodium and potassium between two-kidney, one clip Goldblatt hypertensive rats and sham-operated rats receiving normal diet and tap water (fig. 3). Among all rats treated with or without potassium loading, there was no significant different in serum sodium and potassium by the end of the experiment (table 1).

![Figure 1](http://hyper.ahajournals.org/content/full/351/5/756/F1)

**Figure 1. Changes in systolic blood pressure (BP).** After application of renal artery clip with width of 0.2 mm internal diameter, the BP in rats fed a normal diet and tap water increased progressively. In rats given potassium, the elevation of BP was attenuated. Values are means and bars indicate SD. n = number of animals.
FIGURE 2. Changes in fluid intake and urine volume. In rats treated with potassium, both fluid intake and urine volume significantly increased beginning in the first week of the experiment. Values are means and bars indicate SD. n = number of animals.

FIGURE 3. Changes in urinary excretion of sodium and potassium. In rats treated with potassium, both urinary excretion of sodium and potassium significantly increased beginning on the 5th day of the experiment. Values are means and bars indicate SD. n = number of animals.
POTASSIUM AND RENOVASCULAR HYPERTENSION/Suzuki et al.

Table 1. Effects of Potassium Loading on Serum Sodium and Potassium (Experiment 1)

<table>
<thead>
<tr>
<th>Groups</th>
<th>7th day Sodium (mEq/liter)</th>
<th>7th day Potassium (mEq/liter)</th>
<th>14th day Sodium (mEq/liter)</th>
<th>14th day Potassium (mEq/liter)</th>
<th>28th day Sodium (mEq/liter)</th>
<th>28th day Potassium (mEq/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>149.6 ± 2.2</td>
<td>4.3</td>
<td>138.2 ± 3.4</td>
<td>4.2</td>
<td>139.8 ± 2.7</td>
<td>4.8</td>
</tr>
<tr>
<td>Treated with 0.5% KCl</td>
<td>144.4 ± 5.8</td>
<td>4.5</td>
<td>140.4 ± 5.8</td>
<td>4.9</td>
<td>140.3 ± 5.2</td>
<td>4.9</td>
</tr>
<tr>
<td>Sham-operated</td>
<td>145.4 ± 4.6</td>
<td>4.4</td>
<td>139.2 ± 6.0</td>
<td>4.6</td>
<td>140.5 ± 4.3</td>
<td>4.8</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = number of animals.

PRA and PAC

In rats of Group 1 (without potassium loading), PRA and PAC were markedly increased on Day 7 (p < 0.01) and then further increased toward the end of the experiment. Potassium loading significantly attenuated the increased PRA (p < 0.05) and further enhanced the increased PAC (p < 0.05) in two-kidney, one clip Goldblatt hypertensive rats. In sham-operated rats, there was no difference in PRA and PAC from the control (fig. 4).

Experiment 2

Systolic Blood Pressure

The systolic BP in rats of Group 3 (treated without potassium loading) increased and attained levels of 180 to 200 mm Hg by the end of the experiment. Potassium loading significantly reduced the BP of two-kidney, one clip Goldblatt hypertensive rats (p < 0.05). Two weeks after the potassium treatment, there was significant difference in BP between the two groups with and without potassium loading (p < 0.01) (fig. 5).

Body Weight

There was no difference in growth between the two groups [untreated = 222 ± 6 g (before) to 314 ± 8 g (28th day); treated with 0.5% KCl = 230 ± 8 g (before) to 322 ± 6 g (28th day)].

Fluid Intake, Urine Volume, Urinary Excretion of Sodium and Potassium and Serum Sodium and Potassium

Both fluid intake and urine volume were markedly increased after initiation of potassium loading (fig. 6). Potassium loading resulted in increasing urinary excretion of sodium and potassium (fig. 7). No significant changes in serum sodium and potassium were observed between Groups 3 and 4 (table 2).

PRA and PAC

As observed in Experiment 1, both PRA and PAC were significantly increased 2 weeks after renal artery constriction (p < 0.05). After the administration of potassium, PRA was significantly suppressed (p < 0.05). On the other hand, PAC was further increased by potassium loading (p < 0.05) (fig. 8).
FIGURE 5. Changes in systolic blood pressure (BP). Both groups of rats received tap water to drink for the first 2 weeks. After potassium loading was started, the BP significantly decreased and its elevation was prevented. Values are means and bars indicate SD. n = number of animals.

FIGURE 6. Changes in fluid intake and urine volume: Both groups of rats received tap water to drink for the first 2 weeks. After initiation of potassium loading, urine volume and fluid intake increased significantly. Values are means and bars indicate SD. n = number of animals.

TABLE 2. Effect of Potassium Loading on Serum Sodium and Potassium (Experiment 2)

<table>
<thead>
<tr>
<th>Groups</th>
<th>14th day Serum electrolytes (mEq/liter)</th>
<th>28th day Serum electrolytes (mEq/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Na</td>
<td>K</td>
</tr>
<tr>
<td>Untreated</td>
<td>140.2±4.3</td>
<td>4.7±0.7</td>
</tr>
<tr>
<td>(n = 15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated with 0.5% KCl</td>
<td>140.4±2.8</td>
<td>4.9±0.6</td>
</tr>
<tr>
<td>(n = 15)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD; n = number of animals.
Figure 7. Changes in urinary excretion of sodium and potassium. Both groups of rats received tap water to drink for the first 2 weeks. Administration of potassium resulted in a marked increase of urinary excretion of potassium and sodium. Values are means and bars indicate SD. n = number of animals.

Figure 8. The effect of potassium loading on plasma renin activity (PRA) and plasma aldosterone concentration (PAC): Both groups of rats received tap water to drink for the first 2 weeks. Although PRA in rats treated with potassium was significantly suppressed, PAC was further increased. Values are means and bars indicate SD. n = number of animals.
Discussion

We observed that potassium loading attenuated the development of hypertension and also led to abatement of existing hypertension in two-kidney, one clip Goldblatt hypertensive rats. The antihypertensive effect of potassium was accompanied by massive diuresis and natriuresis, and by suppression of PRA.

Since the first report by Willis in 1679, numerous studies have shown that potassium has diuretic and natriuretic properties. However, the precise mechanism underlying the natriuresis by potassium loading still remains controversial. Young et al. and Bauer and Gaunten speculated that small changes in plasma potassium concentration may be an important factor in the regulation of sodium excretion. However, our results indicate that potassium loading causes no change in serum electrolytes. It is suggested, therefore, that factors other than an increased serum potassium level exert natriuretic effects that are sufficiently potent to produce sustained diuresis during potassium loading.

Experimentally, Young et al. demonstrated that potassium loading in dogs maintained on fixed levels of aldosterone caused a cumulative negative sodium balance and a fall in mean arterial pressure. Our results suggest the possibility that the antihypertensive effect of potassium is mediated by the diuretic and natriuretic properties of this substance. However, the effects of diuretics and of salt restriction on BP are controversial in two-kidney, one clip Goldblatt hypertensive rats, since this type of hypertension is generally considered to be renin dependent. Miksche et al. reported that sodium restriction prevented and reduced the BP of two-kidney, one clip Goldblatt hypertensive rats, while Liard demonstrated that acute sodium depletion by furosemide had no measurable effect on the BP.

The effect of potassium on the renin-angiotensin-aldosterone system is complicated. Potassium can directly inhibit the release of renin by the juxtaglomerular apparatus, and inhibit proximal tubular sodium reabsorption. Decreased proximal sodium reabsorption might result in increased flow to the macula densa, which would suppress renin release according to the macula densa hypothesis of control of renin release, whereas it induces massive diuresis that indirectly stimulates renin secretion. It is well established that potassium loading can directly stimulate the synthesis of aldosterone. We have observed that, in two-kidney, one clip Goldblatt hypertensive rats, potassium loading significantly attenuated the increased PRA and enhanced the increased PAC. Since the potassium loading produced marked natriuresis and diuresis, these results suggest that the effects of potassium on PRA and PAC in this type of hypertension are mediated by a direct effect of potassium on the juxtaglomerular apparatus and the adrenal gland, and by an indirect effect of this substance on the macula densa. Liard found that, in two-kidney, one clip Goldblatt hypertensive rats, the BP decreased rapidly and markedly in response to sodium depletion under conditions of suppression of the renin-angiotensin system. It is suggested, therefore, that potassium loading reduced the BP of this type of hypertension by dual effects, namely, by diuresis and natriuresis and by suppression of the PRA.

Another possibility that would explain the antihypertensive action of potassium is its direct effect on the vascular bed. It is well known that an increase in potassium concentration dilates the resistance vessels and attenuates the vascular contractions induced by vasoactive substances. However, since the vascular reactivity was not examined in the present experiment, no conclusion can be made about this possibility.

Based on the present studies, it is suggested that the elevation of BP in two-kidney, one clip Goldblatt hypertension is attenuated and the increased BP is reduced mainly by diuresis and natriuresis and by suppression of the PRA caused by potassium loading.

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Effect of potassium chloride on the blood pressure in two-kidney, one clip Goldblatt hypertensive rats.
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doi: 10.1161/01.HYP.3.5.566

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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